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=> d history

(FILE 'HOME' ENTERED AT 09:16:09 ON 30 MAY 2007)

FILE 'CAPLUS' ENTERED AT 09:16:24 ON 30 MAY 2007

FILE 'CAPLUS' ENTERED AT 09:34:45 ON 30 MAY 2007

L1 741 S RUTHENIUM AND ("HALF-SANDWICH" OR "BIDENTATE LIGAND")

L2

15 S L1 AND (ANTICANCER OR ANTI-CANCER OR ANTITUMOR OR ANTI-TUMOR

FILE 'CAPLUS' ENTERED AT 10:54:14 ON 30 MAY 2007

=> S RUTHENIUM AND ("HALF-SANDWICH" OR "BIDENTATE LIGAND" or "arene complex")

```
96648 RUTHENIUM
23 RUTHENIUMS
96648 RUTHENIUM
      (RUTHENIUM OR RUTHENIUMS)
347068 "HALF"
5 "HALFS"
7472 "HALVES"
352531 "HALF"
      ("HALF" OR "HALFS" OR "HALVES")
32503 "SANDWICH"
2490 "SANDWICHES"
33985 "SANDWICH"
      ("SANDWICH" OR "SANDWICHES")
1771 "HALF-SANDWICH"
      ("HALF" (W) "SANDWICH")
23951 "BIDENTATE"
129 "BIDENTATES"
24030 "BIDENTATE"
      ("BIDENTATE" OR "BIDENTATES")
321336 "LIGAND"
218553 "LIGANDS"
437245 "LIGAND"
      ("LIGAND" OR "LIGANDS")
6495 "BIDENTATE LIGAND"
      ("BIDENTATE" (W) "LIGAND")
20481 "ARENE"
8251 "ARENES"
24117 "ARENE"
      ("ARENE" OR "ARENES")
1340537 "COMPLEX"
743073 "COMPLEXES"
1633043 "COMPLEX"
      ("COMPLEX" OR "COMPLEXES")
1786 "ARENE COMPLEX"
      ("ARENE" (W) "COMPLEX")
L3      1009 RUTHENIUM AND ("HALF-SANDWICH" OR "BIDENTATE LIGAND" OR "ARENE
      COMPLEX")
```

=> s 13 AND (ANTICANCER OR ANTI-CANCER OR ANTITUMOR OR ANTI-TUMOR
UNMATCHED LEFT PARENTHESIS 'AND (ANTICANCER'

The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s 13 AND (ANTICANCER OR ANTI-CANCER OR ANTITUMOR OR ANTI-TUMOR)

```
40485 ANTICANCER
52 ANTICANCERS
40508 ANTICANCER
      (ANTICANCER OR ANTICANCERS)
450498 ANTI
10 ANTIS
450505 ANTI
      (ANTI OR ANTIS)
316831 CANCER
46566 CANCERS
328765 CANCER
      (CANCER OR CANCERS)
7041 ANTI-CANCER
      (ANTI (W) CANCER)
225899 ANTITUMOR
388 ANTITUMORS
```

225916 ANTITUMOR
(ANTITUMOR OR ANTITUMORS)

450498 ANTI
10 ANTIS

450505 ANTI
(ANTI OR ANTIS)

409084 TUMOR
158477 TUMORS

459104 TUMOR
(TUMOR OR TUMORS)

10344 ANTI-TUMOR
(ANTI(W) TUMOR)

L4 32 L3 AND (ANTICANCER OR ANTI-CANCER OR ANTITUMOR OR ANTI-TUMOR)

=> d 14 1-32 abs ibib hitstr

L4 ANSWER 1 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Relatively little is known about the kinetics or the pharmacol. potential of organometallic complexes of osmium compared to its lighter congeners, iron and ruthenium. We report the synthesis of seven new complexes, $[(\eta^6\text{-arene})\text{Os}(\text{NN})\text{Cl}]^+$, containing different bidentate nitrogen (N,N) chelators, and a dichlorido complex, $[(\eta^6\text{-arene})\text{Os}(\text{N})\text{Cl}_2]$. The X-ray crystal structures of seven complexes are reported: $[(\eta^6\text{-bip})\text{Os}(\text{en})\text{Cl}]\text{PF}_6$ (1PF6), $[(\eta^6\text{-THA})\text{Os}(\text{en})\text{Cl}]\text{BF}_4$ (2BF4), $[(\eta^6\text{-p-cym})\text{Os}(\text{phen})\text{Cl}]\text{PF}_6$ (5PF6), $[(\eta^6\text{-bip})\text{Os}(\text{dppz})\text{Cl}]\text{PF}_6$ (6PF6), $[(\eta^6\text{-bip})\text{Os}(\text{azpy-NMe}_2)\text{Cl}]\text{PF}_6$ (7PF6), $[(\eta^6\text{-p-cym})\text{Os}(\text{azpy-NMe}_2)\text{Cl}]\text{PF}_6$ (8PF6), and $[(\eta^6\text{-bip})\text{Os}(\text{NCCH}_3\text{-N})\text{Cl}_2]$ (9), where THA = tetrahydroanthracene, en = ethylenediamine, p-cym = p-cymene, phen = phenanthroline, bip = biphenyl, dppz = [3,2-a: 2',3'-c]phenazine and azpy-NMe₂ = 4-(2-pyridylazo)-N,N-dimethylaniline. The chelating ligand was found to play a crucial role in enhancing aqueous stability. The rates of hydrolysis at acidic pH* decreased when the primary amine N-donors (NN = en, t_{1/2} = 0.6 h at 318 K) are replaced with π -accepting pyridine groups (e.g., NN = phen, t_{1/2} = 9.5 h at 318 K). The OsII complexes hydrolyze up to 100 times more slowly than their RuII analogs. The pK^a of the aqua adducts decreased with a similar trend (pK^a = 6.3 and 5.8 for en and phen adducts, resp.). $[(\eta^6\text{-bip})\text{Os}(\text{en})\text{Cl}]\text{PF}_6/\text{BF}_4$ (1PF6/BF4) and $[(\eta^6\text{-THA})\text{Os}(\text{en})\text{Cl}]\text{BF}_4$ (2BF4) were cytotoxic toward both the human A549 lung and A2780 ovarian cancer cell lines, with IC₅₀ values of 6-10 μM , comparable to the anticancer drug carboplatin. 1BF4 binds to both the N7 and phosphate of 5'-GMP (ratio of 2:1). The formation constant for the 9-ethylguanine (9EtG) adduct $[(\eta^6\text{-bip})\text{Os}(\text{en})(9\text{EtG})]^{2+}$ was lower for OsII (log K = 3.13) than RuII (log K = 4.78), although the OsII adduct showed some kinetic stability. DNA intercalation of the dppz ligand in 6PF6 may play a role in its cytotoxicity. This work demonstrates that the nature of the chelating ligand can play a crucial role in tuning the chemical and biol. properties of $[(\eta^6\text{-arene})\text{Os}(\text{NN})\text{Cl}]^+$ complexes.

ACCESSION NUMBER: 2007:427928 CAPLUS

TITLE: Chloro Half-Sandwich Osmium(II)
Complexes: Influence of Chelated N,N-Ligands on
Hydrolysis, Guanine Binding, and Cytotoxicity

AUTHOR(S): Peacock, Anna F. A.; Habtemariam, Abraha; Moggach,
Stephen A.; Prescimone, Alessandro; Parsons, Simon;
Sadler, Peter J.

CORPORATE SOURCE: School of Chemistry, University of Edinburgh,
Edinburgh, EH9 3JJ, UK

SOURCE: Inorganic Chemistry (Washington, DC, United States)
(2007), 46(10), 4049-4059

CODEN: INOCAJ; ISSN: 0020-1669

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB D. functional calcns. show that aquation of $[\text{Os}(\eta^6\text{-are-ne})(\text{XY})\text{Cl}]_n^+$ complexes is more facile for complexes in which XY = an anionic O,O-chelated ligand compared to a neutral N,N-chelated ligand, and the mechanism more dissociative in character. The O,O-chelated XY = maltolato (mal) $[\text{M}(\eta^6\text{-p-cym})(\text{mal})\text{Cl}]$ complexes, in which p-cym = p-cymene, M = OsII (1) and RuII (2), were synthesized and the X-ray crystal structures of 1 and 2·2H₂O determined. Their hydrolysis rates were rapid (too fast to follow by NMR spectroscopy). The aqua adduct of the OsII complex 1 was 1.6 pKa units more acidic than that of the RuII complex 2. Dynamic NMR studies suggested that O,O-chelate ring opening occurs on a millisecond timescale in coordinating proton-donor solvents, and loss of chelated mal in aqueous soln. led to the formation of the hydroxo-bridged dimers $[(\eta^6\text{-p-cym})\text{M}(\mu\text{-OH})_3\text{M}(\eta^6\text{-p-cym})]^{2+}$. The proportion of this dimer in solns. of the OsII complex 1 increased with dilution and it predominated at micromolar concns., even in the presence of 0.1 M NaCl (conditions close to those used for cytotoxicity testing). Although 9-ethylguanine (9-EtG) binds rapidly to OsII in 1 and more strongly ($\log K = 4.4$) than to RuII in 2 ($\log K = 3.9$), the OsII adduct $[\text{Os}(\eta^6\text{-p-cym})(\text{mal})-(9\text{EtG})]^{2+}$ was unstable with respect to formation of the hydroxo-bridged dimer at micromolar concns. Such insights into the aqueous solution chemical of metal-arene complexes under biol. relevant conditions will aid the rational design of organometallic anticancer agents.

ACCESSION NUMBER: 2007:365079 CAPLUS
TITLE: Osmium(II) and ruthenium(II) arene maltolato complexes: rapid hydrolysis and nucleobase binding
AUTHOR(S): Peacock, Anna F. A.; Melchart, Michael; Deeth, Robert J.; Habtemariam, Abraha; Parsons, Simon; Sadler, Peter J.
CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK
SOURCE: Chemistry--A European Journal (2007), 13(9), 2601-2613
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB On page 10888, the text should read: "Azpy displays a weak $n \rightarrow \pi^*$ (forbidden) transition at 445 nm, and while this transition was not observed for the other ligands, it may be masked by the intense $\pi \rightarrow \pi^*$ transitions." On page 10888 the text should read: "Upon deprotonation of azpy-OH, the $\pi \rightarrow \pi^*$ transitions shift from 246 and 358 nm to 268 and 435 nm." On page 10889, the caption of Figure 6 is incorrect; the correct caption is given.

ACCESSION NUMBER: 2007:82214 CAPLUS
TITLE: Phenylazo-pyridine and Phenylazo-pyrazole Chlorido Ruthenium(II) Arene Complexes: Arene Loss, Aquation, and Cancer Cell Cytotoxicity. [Erratum to document cited in CA146:206434]
AUTHOR(S): Dougan, Sarah J.; Melchart, Michael; Habtemariam, Abraha; Parsons, Simon; Sadler, Peter J.
CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK
SOURCE: Inorganic Chemistry (2007), 46(4), 1508
CODEN: INOCAJ; ISSN: 0020-1669
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; Errata
LANGUAGE: English
IT INDEXING IN PROGRESS

L4 ANSWER 4 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB An organometallic ruthenium arene anticancer complex with ruthenium (pink ball) chelated by ethylenediamine (blue) is selective for guanine bases on DNA and can bury the non-coordinated Ph ring of its arene ligand (yellow) between bases in the double helix.

ACCESSION NUMBER: 2006:1353118 CAPLUS
DOCUMENT NUMBER: 146:246046
TITLE: Diversity in guanine-selective DNA binding modes for an organometallic ruthenium arene complex
AUTHOR(S): Liu, Hong-Ke; Berners-Price, Susan J.; Wang, Fuyi; Parkinson, John A.; Xu, Jingjing; Bella, Juraj; Sadler, Peter J.
CORPORATE SOURCE: School of Chemistry, The University of Edinburgh, Edinburgh, EH93JJ, UK
SOURCE: Angewandte Chemie, International Edition (2006), 45(48), 8153-8156
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Ru(II) η^6 -arene complexes containing p-cymene (p-cym), tetrahydronaphthalene (thn), benzene (bz), or biphenyl (bip), as the arene, phenylazopyridine derivs. (C₅H₄NN:NC₆H₄R-4; R = H (azpy), OH (azpy-OH), NMe₂ (azpy-NMe₂)) or a phenylazopyrazole derivative (NHC₃H₂NN:NC₆H₄NMe₂-4 (azpyz-NMe₂)) as N,N-chelating ligands and chloride as a ligand, were synthesized (1-16). The complexes are all intensely colored due to metal-to-ligand charge-transfer Ru 4d₆- π^* and intraligand $\pi \rightarrow \pi^*$ transitions (ϵ = 5000-63,700 M⁻¹ cm⁻¹) occurring in the visible region. In the crystal structures of [(η^6 -p-cym)Ru(azpy)Cl]PF₆ (1), [(η^6 -p-cym)Ru(azpy-NMe₂)Cl]PF₆ (5), and [(η^6 -bip)Ru(azpy)Cl]PF₆ (4), the relatively long Ru-N(azo) and Ru-(arene-centroid) distances suggest that phenylazopyridine and arene ligands can act as competitive π -acceptors toward Ru(II) 4d₆ electrons. The pK_a^{*} values of the pyridine nitrogens of the ligands are low (azpy 2.47, azpy-OH 3.06 and azpy-NMe₂ 4.60), suggesting that they are weak σ -donors. This, together with their π -acceptor behavior, serves to increase the pos. charge on Ru, and together with the π -acidic η^6 -arene, partially accounts for the slow decomposition of the complexes via hydrolysis and/or arene loss (t_{1/2} = 9-21 h for azopyridine complexes, 310 K). The pK_a^{*} of the coordinated H₂O in [(η^6 -p-cym)Ru(azpyz-NMe₂)OH₂]²⁺ (13A) is 4.60, consistent with the increased acidity of the Ru center upon coordination to the azo ligand. None of the azpy complexes were cytotoxic toward A2780 human ovarian or A549 human lung cancer cells, but several of the azpy-NMe₂, azpy-OH, and azpyz-NMe₂ complexes were active (IC₅₀ values 18-88 μ M).

ACCESSION NUMBER: 2006:1294354 CAPLUS
DOCUMENT NUMBER: 146:206434
TITLE: Phenylazo-pyridine and Phenylazo-pyrazole Chlorido Ruthenium(II) Arene Complexes: Arene Loss, Aquation, and Cancer Cell Cytotoxicity
AUTHOR(S): Dougan, Sarah J.; Melchart, Michael; Habtemariam, Abraha; Parsons, Simon; Sadler, Peter J.
CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK
SOURCE: Inorganic Chemistry (2006), 45(26), 10882-10894
CODEN: INOCAJ; ISSN: 0020-1669
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS

L4 ANSWER 6 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Ruthenium arene complexes containing bidentate diamine, amino acid and diketone chelate ligands were prepared by a variety of appropriate procedures and examined for cytostatic activity against human cancer cells. Organometallic Ru(II) complexes $[(\eta^6\text{-arene})\text{Ru}(\text{XY})\text{Cl}]_2\text{Z}$, where XY is an N,N- (diamine), N,O- (e.g., amino acidate), or O,O- (e.g., β -diketonate) chelating ligand, the arene ranges from benzene derivs. to fused polycyclic hydrocarbons, and Z is usually PF₆, were prepared by direct or reduction-assisted complexation of arenes, substitution of cycloalkadiene or arene ligands with subsequent complexation of bidentate XY-ligands. The x-ray structures of 13 complexes are reported. All have the characteristic "piano-stool" geometry. The structure-activity relationships was evaluated for cytotoxicity of the prepared complexes against human cancer cells. The complexes most active toward A2780 human ovarian cancer cells contained XY = ethylenediamine (en) and extended polycyclic arenes. Complexes with polar substituents on the arene or XY = bipyridyl derivs. exhibited reduced activity. The activity of the O,O-chelated complexes depended strongly on the substituents and on the arene. For arene = p-cymene, XY = amino acidate complexes were inactive. Complexes were not cross-resistant with cisplatin, and cross-resistance to Adriamycin was circumvented by replacing XY = en with 1,2-phenylenediamine. Some complexes were also active against colon, pancreatic, and lung cancer cells.

ACCESSION NUMBER: 2006:1079231 CAPLUS
 DOCUMENT NUMBER: 146:27919
 TITLE: Structure-Activity Relationships for Cytotoxic Ruthenium(II) Arene Complexes Containing N,N-, N,O-, and O,O-Chelating Ligands
 AUTHOR(S): Habtemariam, Abraha; Melchart, Michael; Fernandez, Rafael; Parsons, Simon; Oswald, Iain D. H.; Parkin, Andrew; Fabbiani, Francesca P. A.; Davidson, James E.; Dawson, Alice; Aird, Rhona E.; Jodrell, Duncan I.; Sadler, Peter J.
 CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK
 SOURCE: Journal of Medicinal Chemistry (2006), 49(23), 6858-6868
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 146:27919
 REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Reaction of $[\text{Ru}(\eta^6\text{-p-cymene})\text{Cl}]_2$ with K[oxine] in CH₂Cl₂ gave $\text{Ru}(\eta^6\text{-p-cymene})(\text{oxine})\text{Cl}$ which on sequential treatment with AgCF₃SO₃ in THF and pyrazole gave title compound, $[\text{Ru}(\eta^6\text{-p-cymene})(\text{oxine})(\kappa^1\text{-Hpz})]\text{CF}_3\text{SO}_3$ (3). The crystal structure and antitumor activity of 3 was determined

ACCESSION NUMBER: 2006:957944 CAPLUS
 DOCUMENT NUMBER: 146:358959
 TITLE: Ruthenium(II)-arene complex with heterocyclic ligands as prospective antitumor agent
 AUTHOR(S): John, Roland O.; Arion, Vladimir B.; Jakupec, Michael A.; Keppler, Bernhard K.
 CORPORATE SOURCE: Institute of Inorganic Chemistry, University of Vienna, Vienna, 1090, Austria
 SOURCE: Metal Ions in Biology and Medicine (2006), 9, 40-45
 CODEN: MIBMCT; ISSN: 1257-2535

PUBLISHER: John Libbey Eurotext
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:358959
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Organometallic ruthenium(II)arene complexes have emerged as promising novel anticancer compds. However, little is known about their mol. mechanism of action. Using Car-Parrinello mol. dynamics (CP-MD), we calculated the free energy profile for the hydrolysis reaction of [(arene)Ru(II)(en)(Cl)] (1) in explicit quantum water. Gas phase CPMD simulations and potential energy calcns. at the DFT and MP2 level of theory rationalize the exclusive chemoselectivity of 1 towards guanine. Three different reaction pathways and the corresponding transition states have been identified. Subsequently, we performed classical MD and mixed QM/MM CPMD simulations to characterize the binding mode of two series of ruthenium(II) arene-complexes to dsDNA. The monofunctional 1 and the bifunctional [(arene)Ru(PTA)(L)2] (2) series of compds. were both bound to a 12-mer. The free energy profile for the reaction of 1 with dsDNA has been obtained. A tailor made force field for compound 1 was derived from our QM/MM trajectories using a new force matching approach. The local and global structural modifications of DNA upon complexation were analyzed in detail. The differences of the DNA-interaction-properties between the two series of compds. are discussed and linked to exptl. observations. In particular, an atomistic description of a Watson-Crick base-pair break upon binding of 2 to dsDNA is proposed (Figure). Fundamental differences between binding of 1 or 2 to single stranded DNA (ssDNA) and dsDNA are rationalized.

ACCESSION NUMBER: 2006:859244 CAPLUS
TITLE: DNA-Binding of ruthenium-arene anticancer drugs
AUTHOR(S): Gossens, Christian; Tavernelli, Ivano; Rothlisberger, Ursula
CORPORATE SOURCE: Institute of Chemical Sciences and Engineering, Federal Institute of Technology Lausanne, Lausanne, 1015, Switz.
SOURCE: Abstracts of Papers, 232nd ACS National Meeting, San Francisco, CA, United States, Sept. 10-14, 2006 (2006), COMP-331. American Chemical Society: Washington, D. C.
CODEN: 69IHRD
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English

L4 ANSWER 9 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Ruthenium arene half-sandwich imidazole, benzimidazole, pyridine and morpholine complexes were prepared and evaluated for their cytotoxicity against tumor cells. Ten complexes [Ru(η^6 -arene)Cl₂(L)], [Ru(η^6 -arene)Cl(L)₂](X), and [Ru(η^6 -arene)(L)₃](X)₂ (η^6 -arene = benzene, p-cymene; L = imidazole-N3, benzimidazole-N3, N-methylimidazole-N3, N-butylimidazole-N3, N-vinylimidazole-N3, N-benzoylimidazole-N3, pyridine, morpholine-N; X = Cl, BF₄, BPh₄) were prepared by reaction of [(arene)₂Ru₂(μ -Cl)₂Cl₂] with the corresponding ligands; the complexes were spectroscopically characterized. The structures of five representative compds. were confirmed by single-crystal x-ray crystallog. anal. All the new compds. were assessed by in vitro screening cytotoxicity assays against murine adenocarcinoma cell lines. The new compds. show essentially the same order of cytotoxicity as the known 1,3,5-triaza-7-phosphaadamantane ruthenium complex (RAPTA). Several of the compds. were selective toward cancer cells in that they were less (or not) cytotoxic toward non-tumorigenic cells that are used to model healthy human cells. Thus,

two of the compds., [Ru(η^6 -p-cymene)Cl(N-vinylimidazole)₂][Cl] and [Ru(η^6 -benzene)(N-methylimidazole)₃][BF₄]₂ have been selected for a more detailed in vivo evaluation.

ACCESSION NUMBER: 2006:784692 CAPLUS
DOCUMENT NUMBER: 145:377456
TITLE: Synthesis, Characterization, and in Vitro Evaluation of Novel Ruthenium(II) η^6 -Arene Imidazole Complexes
AUTHOR(S): Vock, Carsten A.; Sclaro, Claudine; Phillips, Andrew D.; Scopelliti, Rosario; Sava, Gianni; Dyson, Paul J.
CORPORATE SOURCE: Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, CH-1015, Switz.
SOURCE: Journal of Medicinal Chemistry (2006), 49(18), 5552-5561
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:377456
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Reaction of the dimer [(η^5 -C₅Me₅)RhCl(μ_2 -Cl)]₂ with 2 or 4 equiv of the water-soluble phosphine 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (pta) affords [Rh(η^5 -C₅Me₅)(pta)Cl₂] in 73% and [Rh(η^5 -C₅Me₅)(pta)₂Cl]Cl in 77% yields, resp. Both complexes have been characterized in solution by NMR spectroscopy and in the solid state by single-crystal x-ray diffraction, the latter as the chloride and BPh₄-salts. In addition, the rhodium(I) complexes [Rh(η^5 -C₅Me₅)(CO)(pta)] (60% yield) and [Rh(η^5 -C₅H₅)(pta)₂] (30% yield) have been prepared from [Rh(η^5 -C₅Me₅)(CO)₂] and [Rh(η^5 -C₅H₅)(PPh₃)₂], resp., by reaction with pta. An in vitro evaluation of these compds., together with [Os(η^6 -C₁₀H₁₄)(pta)Cl₂] (C₁₀H₁₄ = p-cymene) and the well-characterized antimetastasis drug [Ru(η^6 -C₁₀H₁₄)(pta)Cl₂], RAPTA-C, was undertaken using HT29 colon carcinoma, A549 lung carcinoma, and T47D breast carcinoma cells. In the HT29 cell line, the two nearest congeners to [Ru(η^6 -C₁₀H₁₄)(pta)Cl₂], viz., [Rh(η^5 -C₅Me₅)(pta)Cl₂] and [Os(η^6 -C₁₀H₁₄)(pta)Cl₂], demonstrated very similar cytotoxicity profiles. [Rh(η^5 -C₅Me₅)(pta)Cl₂] proved significantly more cytotoxic in A549 cells and [Rh(η^5 -C₅Me₅)(pta)₂Cl]Cl 3-fold more cytotoxic in T47D cells, both relative to RAPTA-C. These data suggest that the development of organometallic anticancer drugs based on the neighboring elements to ruthenium should not be overlooked.

ACCESSION NUMBER: 2006:672933 CAPLUS
DOCUMENT NUMBER: 145:293173
TITLE: In Vitro Evaluation of Rhodium and Osmium RAPTA Analogues: The Case for Organometallic Anticancer Drugs Not Based on Ruthenium
AUTHOR(S): Dorcier, Antoine; Ang, Wee Han; Bolano, Sandra; Gonsalvi, Luca; Juillerat-Jeannerat, Lucienne; Laurenczy, Gabor; Peruzzini, Maurizio; Phillips, Andrew D.; Zanobini, Fabrizio; Dyson, Paul J.
CORPORATE SOURCE: Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, CH-1015, Switz.
SOURCE: Organometallics (2006), 25(17), 4090-4096
CODEN: ORGND7; ISSN: 0276-7333
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:293173
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS

L4 ANSWER 11 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Optimization of the design of half-sandwich organometallic RuII arene complexes as anticancer agents depends on control of ligand exchange reactions. The aqueous chemical of complexes containing O,O-chelate rings are studied.

The

presence of the four-membered O,O-chelate ring from acetate (AcO) in $[(\eta^6\text{-p-cymene})\text{Ru}(\text{AcO})\text{Cl}]$ was confirmed by x-ray crystallog., but in solution the acetate ligand was labile and the hydroxo-bridged dimer $[(\eta^6\text{-p-cymene})\text{Ru}_2(\mu\text{-OH})_3]^+$ readily formed. The dimer was relatively unreactive towards 9-Et guanine. The tropolonato (trop) complex $[(\eta^6\text{-p-cymene})\text{Ru}(\text{trop})\text{Cl}]$ was stable in aqueous media and the x-ray crystal structure of the aqua adduct $[(\eta^6\text{-p-cymene})\text{Ru}(\text{trop})(\text{H}_2\text{O})]\text{CF}_3\text{SO}_3$, containing a five-membered O,O-chelate ring from trop, was determined. $[(\eta^6\text{-p-cymene})\text{Ru}(\text{trop})\text{Cl}]$ reacted with guanosine to form N7 adducts and with adenosine to form both N7 and N1 adducts. Competitive reactions with guanosine and adenosine gave rise to guanosine:adenosine adducts in a ca. 1.3:1 mol ratio.

ACCESSION NUMBER: 2006:484913 CAPLUS

DOCUMENT NUMBER: 145:167392

TITLE: Ruthenium(II) arene complexes containing four- and five-membered monoanionic O,O-chelate rings

AUTHOR(S): Melchart, Michael; Habtemariam, Abraha; Parsons, Simon; Moggach, Stephen A.; Sadler, Peter J.

CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK

SOURCE: Inorganica Chimica Acta (2006), 359(9), 3020-3028
CODEN: ICHAA3; ISSN: 0020-1693

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 145:167392

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Ruthenium(II) arene anticancer complexes $[(\eta^6\text{-arene})\text{Ru}(\text{en})\text{Cl}]\text{PF}_6$ (arene is hexamethylbenzene, p-cymene, indan; en is ethylenediamine) can catalyze regioselective reduction of NAD⁺ by formate in water to form 1,4-NADH, at pD 7.2, 37°, and in the presence of air. The catalytic activity is markedly dependent on the arene, with the hexamethylbenzene (hmb) complex showing the highest activity. For $[(\eta^6\text{-hmb})\text{Ru}(\text{en})\text{Cl}]\text{PF}_6$, the rate of reaction is independent of NAD⁺ concentration

and

shows saturation kinetics with respect to formate concentration. A K_m value of 58 mM

and a turnover frequency at saturation of 1.46 h⁻¹ were observed. Removal of chloride and performing the reaction under argon led to higher reaction rates. Lung cancer cells (A549) were found to be remarkably tolerant to formate even at millimolar concns. The possibility of using ruthenium arene complexes coadministered with formate as catalytic drugs is discussed.

ACCESSION NUMBER: 2006:431631 CAPLUS

DOCUMENT NUMBER: 145:119261

TITLE: Catalysis of regioselective reduction of NAD⁺ by ruthenium(II) arene complexes under biologically relevant conditions

AUTHOR(S): Yan, Yaw Kai; Melchart, Michael; Habtemariam, Abraha; Peacock, Anna F. A.; Sadler, Peter J.

CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK

SOURCE: JBIC, Journal of Biological Inorganic Chemistry
(2006), 11(4), 483-488
CODEN: JJBCFA; ISSN: 0949-8257
PUBLISHER: Springer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB The OsII arene ethylenediamine (en) complexes $[(\eta^6\text{-biphenyl})\text{Os}(\text{en})\text{Cl}][\text{Z}]$, $\text{Z} = \text{BPh}_4$ (4) and BF_4 (5), are inactive toward A2780 ovarian cancer cells despite 4 being isostructural with an active RuII analog, 4R. Hydrolysis of 5 occurred 40 times more slowly than 4R. The aqua adduct, 5A has a low pK_a (6.3) compared to that of $[(\eta^6\text{-biphenyl})\text{Ru}(\text{en})(\text{OH}_2)]^{2+}$ (7.7) and is therefore largely in the hydroxo form at physiolo. pH. The rate and extent of reaction of 5 with 9-ethylguanine were also less than those of 4R. The authors replaced the neutral en ligand by anionic acetylacetonate (acac). The complexes $[(\eta^6\text{-arene})\text{Os}(\text{acac})\text{Cl}]$, arene = biphenyl (6), benzene (7), and p-cymene (8), adopt piano-stool structures similar to those of the RuII analogs and form weak dimers through intermol. (arene)C-H...O(acac) H-bonds. Remarkably, these OsII acac complexes undergo rapid hydrolysis to produce not only the aqua adduct, $[(\eta^6\text{-arene})\text{Os}(\text{acac})(\text{OH}_2)]^+$, but also the hydroxo-bridged dimer, $[(\eta^6\text{-arene})\text{Os}(\mu\text{-OH})_2\text{Os}(\eta^6\text{-arene})]^+$. The pK_a values for the aqua adducts 6A, 7A, and 8A (7.1, 7.3, and 7.6, resp.) are lower than that for $[(\eta^6\text{-p-cymene})\text{Ru}(\text{acac})(\text{OH}_2)]^+$ (9.4). Complex 8A rapidly forms adducts with 9-ethylguanine and adenosine, but not with cytidine or thymidine. Despite their reactivity toward nucleobases, complexes 6-8 were inactive toward A549 lung cancer cells. This is attributable to rapid hydrolysis and formation of unreactive hydroxo-bridged dimers which, surprisingly, were the only species present in aqueous solution at biol. relevant

concns. Hence, the choice of chelating ligand in OsII (and RuII) arene complexes can have a dramatic effect on hydrolysis behavior and nucleobase binding and provides a means of tuning the reactivity and the potential for discovery of anticancer complexes.

ACCESSION NUMBER: 2006:38977 CAPLUS
DOCUMENT NUMBER: 144:285767
TITLE: Tuning the Reactivity of Osmium(II) and Ruthenium(II) Arene Complexes under Physiological Conditions
AUTHOR(S): Peacock, Anna F. A.; Habtemariam, Abraha; Fernandez, Rafael; Walland, Victoria; Fabbiani, Francesca P. A.; Parsons, Simon; Aird, Rhona E.; Jodrell, Duncan I.; Sadler, Peter J.
CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK
SOURCE: Journal of the American Chemical Society (2006), 128(5), 1739-1748
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:285767
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Organometallic compds. offer broad scope for the design of therapeutic agents, but this avenue has yet to be widely explored. A key concept in the design of anticancer complexes is optimization of chemical reactivity to allow facile attack on the target site (e.g., DNA) yet avoid

attack on other sites associated with unwanted side effects. How this result can be achieved for monofunctional "piano-stool" ruthenium(II) arene complexes of the type $[(\eta^6\text{-arene})\text{Ru}(\text{ethylenediamine})(\text{X})]_{n+}$ was discussed. A potentially important activation mechanism for reactions with biomols. is hydrolysis. D. functional calcs. suggested that aquation (substitution of X by H₂O) occurs by a concerted ligand interchange mechanism. The kinetics and equilibrium for hydrolysis of 21 complexes, containing, as X, halides and pseudohalides, pyridine derivs., and a thiolate, together with benzene (bz) or a substituted bz as arene, using UV-visible spectroscopy, HPLC, and electrospray MS was studied. The x-ray structures of six complexes are reported. In general, complexes that hydrolyze either rapidly {e.g., X = halide [arene = hexamethylbenzene (hmb)]} or moderately slowly [e.g., X = azide, dichloropyridine (arene = hmb)] are active toward A2780 human ovarian cancer cells, whereas complexes that do not aquate (e.g., X = py) are inactive. An intriguing exception is the X = thiophenolate complex, which undergoes little hydrolysis and appears to be activated by a different mechanism. The ability to tune the chemical reactivity of this class of organometallic ruthenium arene compds. should be useful in optimizing their design as anticancer agents.

ACCESSION NUMBER: 2006:9229 CAPLUS
 DOCUMENT NUMBER: 144:233191
 TITLE: Controlling ligand substitution reactions of organometallic complexes: Tuning cancer cell cytotoxicity
 AUTHOR(S): Wang, Fuyi; Habtemariam, Abraha; van der Geer, Erwin P. L.; Fernandez, Rafael; Melchart, Michael; Deeth, Robert J.; Aird, Rhona; Guichard, Sylvie; Fabbiani, Francesca P. A.; Lozano-Casal, Patricia; Oswald, Iain D. H.; Jodrell, Duncan I.; Parsons, Simon; Sadler, Peter J.
 CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2005), 102(51), 18269-18274
 CODEN: PNASA6; ISSN: 0027-8424
 PUBLISHER: National Academy of Sciences
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 144:233191
 REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB A new series of organometallic ruthenium(II)-arene compds. of the type $\text{RuCl}_2(\eta^6\text{-arene})(\text{phosphine})$ (phosphine = 1,3,5-triaza-7-phosphaadamantane, PTA, and 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane, DAPTA) with different potential hydrogen-bonding functionalities on the arene ligand have been prepared and studied for their antitumor activity. Cell viability studies using the TS/A mouse adenocarcinoma cancer cell line and the nontumorigenic HBL-100 human mammary cell line, combined with uptake detns., are compared to the nonfunctionalized analogs, previously shown to be active on solid metastasizing tumors. The reactivity of the functionalized RAPTA compds. with a 14-mer oligonucleotide (established by mass spectrometry) has been rationalized by DFT calcs., which indicate that environmental factors are important. The structure of $[\text{RuCl}(\eta^6\text{-C}_6\text{H}_5(\text{CH}_2)_2\text{NH}_2)(\text{PTA})][\text{BF}_4]$ was investigated by x-ray crystallog. and DFT calcs.

ACCESSION NUMBER: 2006:7 CAPLUS
 DOCUMENT NUMBER: 144:233188
 TITLE: Influence of Hydrogen-Bonding Substituents on the Cytotoxicity of RAPTA Compounds
 AUTHOR(S): Scolaro, Claudine; Geldbach, Tilmann J.; Rochat, Sebastien; Dorcier, Antoine; Gossens, Christian;

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Bergamo, Alberta; Cocchietto, Moreno; Tavernelli, Ivano; Sava, Gianni; Rothlisberger, Ursula; Dyson, Paul J.

CORPORATE SOURCE: Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, CH-1015, Switz.

SOURCE: Organometallics (2006), 25(3), 756-765
CODEN: ORGND7; ISSN: 0276-7333

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 144:233188

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB New half-sandwich RuII-[9]aneS3 complexes ([9]aneS3 = 1,4,7-trithiacyclononane), [RuCl₂(PTA)([9]aneS₃)] (4), [RuCl(PTA)₂([9]aneS₃)] [OTf] (5), [RuCl(en)([9]aneS₃)] [OTf] (6), [RuCl(enac)([9]aneS₃)] [OTf] (7), [RuCl(bipy)([9]aneS₃)] [OTf] (8), and [Ru(DMSO-S)(bipy)([9]aneS₃)] [OTf]₂ (9) [PTA = 1,3,5-triaza-7-phosphaadamantane; enac = 1,2-bis(isopropyleneimino)ethane; OTf = CF₃SO₃-] were prepared from Ru-[9]aneS₃-DMSO precursors and structurally characterized, both in solution and in the solid state by x-ray crystallog. Some of them are analogs of known cytotoxic organometallic RuII-(η^6 -arene) and RuII-(η^5 -cyclopentadienyl) compds., in which the aromatic fragment is replaced by the S macrocycle 1,4,7-trithiacyclononane, while the rest of the coordination sphere is left unchanged. Similarly to the aromatic analogs for which data are available, in aqueous solution the Ru-[9]aneS₃ complexes (with the exception of 5)

hydrolyze a chloride (or a DMSO in the case of 9) to give the corresponding aqua species. This process is rapidly reversed in the presence of free chloride, and coordination of phosphate probably occurs to the aquo species in phosphate buffered solns. at physiol. pH. Preliminary in vitro tests performed on complexes 4-6 against the mouse adenocarcinoma cancer cell line (TS/A) and the human mammary normal cell line (HBL-100) showed that, in general, the Ru-[9]aneS₃ compds. have a cytotoxicity comparable to that of the corresponding organometallic analogs. Probably the aromatic fragment of the piano-stool RuII compds. is not an essential feature for the in vitro anticancer activity, and it might be effectively replaced by another face-capping ligand with a low steric demand, such as [9]aneS₃.

ACCESSION NUMBER: 2005:1056291 CAPLUS

DOCUMENT NUMBER: 144:204530

TITLE: Is the aromatic fragment of piano-stool ruthenium compounds an essential feature for anticancer activity? The development of New RuII-[9]aneS₃ analogues

AUTHOR(S): Serli, Barbara; Zangrando, Ennio; Gianferrara, Teresa; Scolaro, Claudine; Dyson, Paul J.; Bergamo, Alberta; Alessio, Enzo

CORPORATE SOURCE: Dipartimento di Scienze Chimiche, University of Trieste, Trieste, 34127, Italy

SOURCE: European Journal of Inorganic Chemistry (2005), (17), 3423-3434
CODEN: EJICFO; ISSN: 1434-1948

PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 144:204530

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB A review. Our work has shown that certain ruthenium(II) arene complexes exhibit promising anticancer activity in vitro and in vivo. The complexes are stable and water-soluble, and their frameworks provide considerable scope for optimizing the design, both in terms of their biol. activity and for minimizing side-effects by variations in the arene and the other coordinated ligands. Initial studies on amino acids and nucleotides suggest that kinetic and thermodyn. control over a wide spectrum of reactions of Ru(II) arene complexes with biomols. can be achieved. These Ru(II) arene complexes appear to have an altered profile of biol. activity in comparison with metal-based anticancer complexes currently in clin. use or on clin. trial.

ACCESSION NUMBER: 2005:1039145 CAPLUS
DOCUMENT NUMBER: 143:482733
TITLE: Organometallic chemistry, biology and medicine: ruthenium arene anticancer complexes
AUTHOR(S): Yan, Yaw Kai; Melchart, Michael; Habtemariam, Abraha; Sadler, Peter J.
CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK
SOURCE: Chemical Communications (Cambridge, United Kingdom) (2005), (38), 4764-4776
CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB The antitumor activity of the organometallic ruthenium (II)-arene complexes, RuCl₂(η⁶-arene)(PTA), (arene = p-cymene, toluene, benzene, benzo-15-crown-5, 1-ethylbenzene-2,3-dimethylimidazolium tetrafluoroborate, Et benzoate, hexamethylbenzene; PTA = 1,3,5-triaza-7-phosphaadamantane), abbreviated RAPTA, has been evaluated. In vitro biol. expts. demonstrate that these compds. are active toward the TS/A mouse adenocarcinoma cancer cell line whereas cytotoxicity on the HBL-100 human mammary (nontumor) cell line was not observed at concns. up to 0.3 mM, which indicates selectivity of these ruthenium(II)-arene complexes to cancer cells. Analogs of the RAPTA compds., in which the PTA ligand is methylated, have also been prepared, and these prove to be cytotoxic toward both cell lines. RAPTA-C and the benzene analog RAPTA-B were selected for in vivo expts. to evaluate their anticancer and antimetastatic activity. The results show that these complexes can reduce the growth of lung metastases in CBA mice bearing the MCa mammary carcinoma in the absence of a corresponding action at the site of primary tumor growth. Pharmacokinetic studies of RAPTA-C indicate that ruthenium is rapidly eliminated from the organs and the bloodstream.

ACCESSION NUMBER: 2005:434823 CAPLUS
DOCUMENT NUMBER: 143:125821
TITLE: In Vitro and in Vivo Evaluation of Ruthenium (II)-Arene PTA Complexes
AUTHOR(S): Scolaro, Claudine; Bergamo, Alberta; Brescacin, Laura; Delfino, Riccarda; Cocchiello, Moreno; Laurenczy, Gabor; Geldbach, Tilmann J.; Sava, Gianni; Dyson, Paul J.
CORPORATE SOURCE: Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, CH-1015, Switz.
SOURCE: Journal of Medicinal Chemistry (2005), 48(12), 4161-4171
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal

LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:125821
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Organometallic Ru(II)-arene complexes are currently attracting increasing interest as anticancer compds. with the potential to overcome drawbacks of traditional drugs like cisplatin with respect to resistance, selectivity, and toxicity. Rational design of new potential pharmaceutical compds. requires a detailed understanding of structure-property relations at an atomic level. In vacuo d. functional theory (DFT) calcns., classical MD, and mixed QM/MM Car-Parrinello MD explicit solvent simulations to rationalize the binding mode of two series of anticancer Ru(II) arene complexes to double-stranded DNA (dsDNA) was performed. Binding energies between the metal centers and the surrounding ligands as well as proton affinities were calculated using DFT. Results support a pH-dependent mechanism for the activity of the RAPTA [Ru(η^6 -arene)X₂(pta)] (pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane) compds. Adducts of the bifunctional RAPTA and the monofunctional [Ru(η^6 -p-cymene)Xen]⁺ series of compds. with the DNA sequence d(CCTCTG*G*TCTCC)/d(GGAGACCAGAGG), where G* are guanosine bases that bind to the Ru compds. through their N(7) atom, were studied. The resulting binding sites were characterized in QM/MM mol. dynamics simulations showing that DNA can easily adapt to accommodate the Ru compds.

ACCESSION NUMBER: 2005:386195 CAPLUS
DOCUMENT NUMBER: 144:254216
TITLE: Rational design of organo-ruthenium anticancer compounds
AUTHOR(S): Gossens, Christian; Tavernelli, Ivano; Rothlisberger, Ursula
CORPORATE SOURCE: Laboratory of Computational Chemistry and Biochemistry, Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne EPFL-BCH, Lausanne, CH-1015, Switz.
SOURCE: Chimia (2005), 59(3), 81-84
CODEN: CHIMAD; ISSN: 0009-4293
PUBLISHER: Swiss Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Ru(II) and Os(II) p-cymene dichloride complexes with either a pta (1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane) or [pta-Me]Cl ligand which exhibit anticancer activity were prepared and characterized by ¹H and ³¹P NMR spectroscopy and mass spectrometry. Three of the complexes, viz. [Os(η^6 -p-cymene)Cl₂(pta)] and [M(η^6 -p-cymene)Cl₂(pta-Me)]Cl (M = Ru, Os), also were characterized by single-crystal x-ray diffraction. The pta complexes are selective anticancer agents, whereas the pta-Me⁺ complexes are indiscriminate and damage both cancer and healthy cells but represent models for the protonated pta adduct which was implicated in drug activity. To establish a link between their biol. activity and the effect they have on DNA (a likely in vivo target), the reactivity of the complexes toward a 14-mer oligonucleotide (5'-ATACATGGTACATA-3') was studied using electrospray ionization mass spectrometry. The complexes bind to the oligonucleotide with loss of chloride and in some cases loss of the arene. Loss of arene appears to be most facile with the Ru-pta complexes but also takes place with the Ru-pta-Me complexes, whereas arene loss is not observed for the Os complexes. As pH is reduced, increased binding to the oligonucleotide is observed, as evidenced from mass spectrometric relative intensities. Binding energies between the metal centers and the surrounding ligands were calculated using d.

functional theory (DFT). The calculated energies rationalize the exptl. observed

tendencies for arene loss and show that the pta ligands are relatively strongly bound. Exchange of metal center (Ru vs. Os), methylation or protonation of the pta ligand, or change of the arene (p-cymene vs. benzene) results in significant differences in the metal-arene binding energies while leaving the metal-phosphine bond strength essentially unchanged. Significantly lower binding energies and reduced hapticity are predicted for the exchange of arene by nucleobases. The latter show higher binding energies for N σ -bonding than for π -bonding.

ACCESSION NUMBER: 2005:248426 CAPLUS
DOCUMENT NUMBER: 143:7797
TITLE: Binding of Organometallic Ruthenium(II) and Osmium(II) Complexes to an Oligonucleotide: A Combined Mass Spectrometric and Theoretical Study
AUTHOR(S): Dorcier, Antoine; Dyson, Paul J.; Gossens, Christian; Rothlisberger, Ursula; Scopelliti, Rosario; Tavernelli, Ivano
CORPORATE SOURCE: Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, CH-1015, Switz.
SOURCE: Organometallics (2005), 24(9), 2114-2123
CODEN: ORGND7; ISSN: 0276-7333
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:7797
REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB We analyzed DNA duplexes modified at central guanine residues by monofunctional Ru(II) arene complexes $[(\eta^6\text{-arene})\text{Ru(II)(en)(Cl)}]^+$ (arene = tetrahydroanthracene or p-cymene, Ru-THA or Ru-CYM, resp.). These two complexes were chosen as representatives of two different classes of Ru(II) arene compds. for which initial studies revealed different binding modes: one that may involve DNA intercalation (tricyclic-ring Ru-THA) and the other (mono-ring Ru-CYM) that may not. Ru-THA is .apprx.20 times more toxic to cancer cells than Ru-CYM. The adducts of Ru-THA and Ru-CYM have contrasting effects on the conformation, thermodyn. stability, and polymerization of DNA in vitro. In addition, the adducts of Ru-CYM are removed from DNA more efficiently than those of Ru-THA. Interestingly, the mammalian nucleotide excision repair system has low efficiency for excision of ruthenium adducts compared to cisplatin intra-strand crosslinks.

ACCESSION NUMBER: 2005:63663 CAPLUS
DOCUMENT NUMBER: 143:300867
TITLE: Conformation of DNA Modified by Monofunctional Ru(II) Arene Complexes: Recognition by DNA Binding Proteins and Repair. Relationship to Cytotoxicity
AUTHOR(S): Novakova, Olga; Kasparkova, Jana; Bursova, Vendula; Hofr, Ctirad; Vojtiskova, Marie; Chen, Haimei; Sadler, Peter J.; Brabec, Viktor
CORPORATE SOURCE: Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, CZ-61265, Czech Rep.
SOURCE: Chemistry & Biology (2005), 12(1), 121-129
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB A novel class of ruthenium (III) complexes of formulas $K[Ru(sar)2Cl_2] \cdot 1/2H_2O$ and $K_2[Ru(dmglly)Cl_4] \cdot 2H_2O$, containing bidentate chelates N-methylglycine (sarcosine, sar) or N,N-dimethylglycine (dmglly) and addnl. chloro ligands were synthesized. The complexes have been obtained by direct reaction of ruthenium(III) chloride with corresponding bidentate ligand followed by addition of base (KOH). These new complexes were characterized by elemental anal., IR and electronic absorption spectroscopy. As astrocytomas, the most common of all brain tumors, are still very difficult to treat, we examined the influence of newly synthesized ruthenium-based complexes, as well as the earlier synthesized analog platinum(IV) complexes $[Pt(dmglly)2Cl_2]$, $[Pt(sar)2Br_2]$ and $[Pt(dmglly)2Br_2]$, on rat astrocytoma C6 cells in vitro. Among these complexes only $K_2[Ru(dmglly)Cl_4] \cdot 2H_2O$ and $[Pt(dmglly)2Br_2]$ markedly inhibited the viability of non-confluent C6 cells. Furthermore, only complex $K_2[Ru(dmglly)Cl_4] \cdot 2H_2O$ was able to reduce viability in confluent C6 cultures. Importantly, this complex was not toxic to primary rat astrocytes or macrophages. Having in mind that appropriate chemotherapy should be effective against tumor cells without harming normal tissues, complex $K_2[Ru(dmglly)Cl_4] \cdot 2H_2O$ could be a promising agent for developing therapeutics against astrocytomas.

ACCESSION NUMBER: 2004:975456 CAPLUS

DOCUMENT NUMBER: 142:106771

TITLE: Novel ruthenium complex
 $K_2[Ru(dmglly)Cl_4] \cdot 2H_2O$ is toxic to C6 astrocytoma cell line, but not to primary rat astrocytes

AUTHOR(S): Djinovic, Vesna; Momcilovic, Miljana; Grguric-Sipka, Sanja; Trajkovic, Vladimir; Stojkovic, Marija Mostarica; Miljkovic, Djordje; Sabo, Tibor

CORPORATE SOURCE: Faculty of Chemistry, University of Belgrade, Belgrade, 11000,

SOURCE: Journal of Inorganic Biochemistry (2004), 98(12), 2168-2173

CODEN: JIBIDJ; ISSN: 0162-0134

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB The chelating ligand XY in RuII anticancer complexes $[Ru(\eta^6\text{-arene})(XY)Cl]n+$ has a major influence on the rate and extent of aquation, the pKa of the aqua adduct, and the rate and selectivity of binding to nucleobases. Replacement of neutral ethylenediamine (en) by anionic acetylacetonate (acac) as the chelating ligand increases the rate and extent of hydrolysis, the pKa of the aqua complex (from 8.25 to 9.41 for arene = p-cymene), and changes the nucleobase specificity. For the complexes containing the H-bond donor en, there is exclusive binding to N7 of guanine in competitive nucleobase reactions, and in the absence of guanine, binding to cytosine or thymine but not to adenine. In contrast, when XY is the H-bond acceptor acac, the overall affinity for adenosine (N7 and N1 binding) is comparable to that for guanosine, but there is little binding to cytidine or thymidine.

ACCESSION NUMBER: 2004:900041 CAPLUS

DOCUMENT NUMBER: 142:38379

TITLE: Use of chelating ligands to tune the reactive site of half-sandwich ruthenium (II)-arene anticancer complexes

AUTHOR(S): Fernandez, Rafael; Melchart, Michael; Habtemariam, Abraha; Parsons, Simon; Sadler, Peter J.

CORPORATE SOURCE: School of Chemistry, University of Edinburgh, Edinburgh, EH9 3 JJ, UK

SOURCE: Chemistry--A European Journal (2004), 10(20),

5173-5179

CODEN: CEUJED; ISSN: 0947-6539

PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:38379
REFERENCE COUNT: 38

THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB The bidentate ligand 2-phenylazopyridine (azpy) can -
in theory - give rise to five different isomeric complexes [Ru(azpy)₂Cl₂],
of which three were known since 1980. The mol. structures of the
cis-dichlorobis(2-phenylazopyridine) Ru(II) complexes α -
[Ru(azpy)₂Cl₂] and β -[Ru(azpy)₂Cl₂] (in which the coordinating
pyridine N atoms are in mutually trans and cis positions, resp., while the
azo N atoms are in mutually cis positions) were unambiguously determined in the
early 1980s. The 3rd isomer, γ -[Ru(azpy)₂Cl₂], has for two decades,
erroneously, been assumed to be the all-trans isomer. In a recent
communication for this γ isomer the chloride ions are indeed in a
trans geometry, but the pyridine N and azo N atoms of the two azpy ligands
are in mutually cis geometries. The isolation of a 4th isomer is
presented, the hitherto unknown δ -[Ru(azpy)₂Cl₂]. The isomeric
structure of δ -[Ru(azpy)₂Cl₂] was determined by 1H-NMR spectroscopy and
single-crystal x-ray diffraction anal., and is the all-trans isomer. The
bis(azpy)-Ru(II) isomers are of interest because of the pronounced
cytotoxicity they exhibit against tumor cell lines and could be very
useful in the search for structure-activity relations of antitumor
-active Ru complexes, as among the isomers there is a significant
difference in activity. It is of paramount importance to have a good
understanding of the structural and spectroscopic properties of these
complexes, which in this paper are compared and discussed, with a
particular emphasis on 1-dimensional and 2-dimensional 1H NMR
spectroscopies.

ACCESSION NUMBER: 2004:63559 CAPLUS

DOCUMENT NUMBER: 140:331268

TITLE: Dichlorobis(2-phenylazopyridine)ruthenium
(II) complexes: characterization, spectroscopic and
structural properties of four isomers

AUTHOR(S): Velders, Aldrik H.; van der Schilden, Karlijn; Hotze,
Anna C. G.; Reedijk, Jan; Kooijman, Huub; Spek,
Anthony L.

CORPORATE SOURCE: Leiden Institute of Chemistry, Gorlaeus Laboratories,
Leiden University, Leiden, 2300 RA, Neth.

SOURCE: Dalton Transactions (2004), (3), 448-455

CODEN: DTARAF; ISSN: 1477-9226

PUBLISHER: Royal Society of Chemistry

DOCUMENT TYPE: Journal

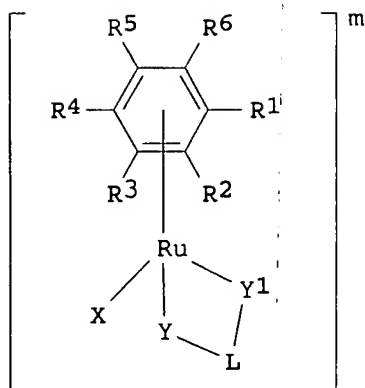
LANGUAGE: English

OTHER SOURCE(S): CASREACT 140:331268

REFERENCE COUNT: 43
THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

GI



I

AB The preparation of half-sandwich ruthenium(II) compds. I (R1-R6 = independent to each other H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, hydroxy(C1-6)alkyl, amino(C1-6)alkyl, halo, alkoxycarbonyl, aminocarbonyl, SO₃H, aminosulfonyl, aryloxy, C1-6 alkoxy, C1-6 alkylthio, etc.; X = O-, N-, S- donor ligand, halo, etc.; Y-L-Y1 = bidentate ligand bearing neg. charge, etc.; m = -1, 0, 1), useful in the treatment and/or prevention of cancer, is described. Thus, reaction of [(η⁶-p-cymene)RuCl₂]₂ with sodium acetylacetonate monohydrate in Me₂CO gave 59% title compound, [(η⁶-p-cymene)RuCl(H₃CCOCHCOCH₃-O,O)].

ACCESSION NUMBER: 2004:41485 CAPLUS

DOCUMENT NUMBER: 140:94145

TITLE: Preparation of half-sandwich ruthenium anticancer complexes

INVENTOR(S): Sadler, Peter John; Fernandez Lainez, Rafael; Habtemariam, Abraba; Melchart, Michael; Jodrell, Duncan Ian

PATENT ASSIGNEE(S): The University Court, the University of Edinburgh, UK

SOURCE: PCT Int. Appl., 46 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005304	A1	20040115	WO 2003-GB2879	20030704
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2491640	A1	20040115	CA 2003-2491640	20030704
AU 2003251159	A1	20040123	AU 2003-251159	20030704
BR 2003012470	A	20050426	BR 2003-12470	20030704
EP 1558620	A1	20050803	EP 2003-762788	20030704
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1665826	A	20050907	CN 2003-816000	20030704
JP 2005536487	T	20051202	JP 2004-518958	20030704

ZA 2005000908	A	20060329	ZA 2005-908	20050201
NO 2005000640	A	20050322	NO 2005-640	20050204
US 2006058270	A1	20060316	US 2005-520239	20050718
PRIORITY APPLN. INFO.:			GB 2002-15526	A 20020705
			WO 2003-GB2879	W 20030704

OTHER SOURCE(S): CASREACT 140:94145; MARPAT 140:94145
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN
AB The recognition of nucleic acid derivs. by organometallic ruthenium(II) arene anticancer complexes of the type $[(\eta^6\text{-arene})\text{Ru(II)(en)X}]$ (en = ethylenediamine, arene = biphenyl (Bip), tetrahydroanthracene (THA), dihydroanthracene (DHA), p-cymene (Cym) or benzene (Ben), X = Cl⁻ or H₂O) was studied using ¹H, ³¹P and ¹⁵N (15N-en) NMR spectroscopy. For mononucleosides, $[(\eta^6\text{-Bip})\text{Ru(en)}]^{2+}$ binds only to N7 of guanosine, to N7 and N1 of inosine, and to N3 of thymidine. Binding to N3 of cytidine was weak, and almost no binding to adenosine was observed. The reactivity of the various binding sites of nucleobases toward Ru at neutral pH decreased in the order G(N7) > I(N7) > I(N1), T(N3) > C(N3) > A(N7), A(N1). Therefore, pseudo-octahedral diamino Ru(II) arene complexes are much more highly discriminatory between G and A bases than square-planar Pt(II) complexes. Such site-selectivity appears to be controlled by the en NH₂ groups, which H-bond with exocyclic oxygens but are nonbonding and repulsive toward exocyclic amino groups of the nucleobases. For reactions with mononucleotides, the same pattern of site selectivity was observed, but, in addition, significant amts. of the 5'-phosphate-bound species (40-60%) were present at equilibrium for 5'-TMP, 5'-CMP and 5'-AMP. In contrast, no binding to the phosphodiester groups of 3', 5'-cyclic-GMP (cGMP) or cAMP was detected. Reactions with nucleotides proceeded via aquation of $[(\eta^6\text{-arene})\text{Ru(en)Cl}]^+$, followed by rapid binding to the 5'-phosphate, and then rearrangement to give N7, N1, or N3-bound products. Small amts. of the dinuclear species, e.g., Ru-O(PO₃)GMPN7-Ru, Ru-O(PO₃)IMPNI-Ru, Ru-O(PO₃)TMPN3-Ru, Ru-N7IMPNI-Ru, and Ru-N7InoN1-Ru were also detected. In competitive binding expts. for $[(\eta^6\text{-Bip})\text{Ru(en)Cl}]^+$ with 5'-GMP vs. 5'-AMP or 5'-CMP or 5'-TMP, the only final adduct was $[(\eta^6\text{-Bip})\text{Ru(en)(N7-GMP)}]$. Ru-H₂O species were more reactive than Ru-OH species. The presence of Cl⁻ or phosphate in neutral solution significantly decreased the rates of Ru-N7 binding through competitive coordination to Ru. In kinetic studies (pH 7.0, 298 K, 100 mM NaClO₄), the rates of reaction of cGMP with $\{(\eta^6\text{-arene})\text{Ru(II)(en)X}\}^+$ (X = Cl⁻ or H₂O) decreased in the order: THA > Bip > DHA >> Cym > Ben, suggesting that N7-binding is promoted by favorable arene-purine hydrophobic interactions in the associative transition state. These findings have revealed that the diamine NH₂ groups, the hydrophobic arene, and the chloride leaving group have important roles in the novel mechanism of recognition of nucleic acids by Ru arene complexes, and will aid the design of more effective anticancer complexes, as well as new site-specific DNA reagents.

ACCESSION NUMBER: 2002:894426 CAPLUS
DOCUMENT NUMBER: 138:106822
TITLE: Highly Selective Binding of Organometallic Ruthenium Ethylenediamine Complexes to Nucleic Acids: Novel Recognition Mechanisms
AUTHOR(S): Chen, Haimei; Parkinson, John A.; Morris, Robert E.; Sadler, Peter J.
CORPORATE SOURCE: Department of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK
SOURCE: Journal of the American Chemical Society (2003), 125(1), 173-186
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

OTHER SOURCE(S): CASREACT 138:106822
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Ruthenium complexes offer the potential of reduced toxicity, a novel mechanism of action, non-cross resistance, and a different spectrum of activity compared to Pt containing compds. Thirteen novel Ru(II) organometallic arene complexes were evaluated for activity (in vitro and in vivo) in models of human ovarian cancer, and cross-resistance profiles established in cisplatin and multi-drug-resistant variants. A broad range of IC50 values was obtained (0.5 to >100 µM) in A2780 parental cells with 2 compds. (RM175 and HC29) equipotent to carboplatin (6 µM), and the most active compound (HC11) equipotent to cisplatin (0.6 µM). Stable bi-dentate chelating ligands (ethylenediamine), a more hydrophobic arene ligand (tetrahydroanthracene) and a single ligand exchange center (chloride) were associated with increased activity. None of the 6 active Ru(II) compds. were cross-resistant in the A2780cis cell line, demonstrated to be 10-fold resistant to cisplatin/carboplatin by a mechanism involving, at least in part, silencing of MLH1 protein expression via methylation. Varying degrees of cross-resistance were observed in the P-170 glycoprotein overexpressing multi-drug-resistant cell line 2780AD that could be reversed by co-treatment with verapamil. In vivo activity was established with RM175 in the A2780 xenograft together with non-cross-resistance in the A2780cis xenograft and a lack of activity in the 2780AD xenograft. High activity coupled to non cross-resistance in cisplatin resistant models merit further development of this novel group of anticancer compds.

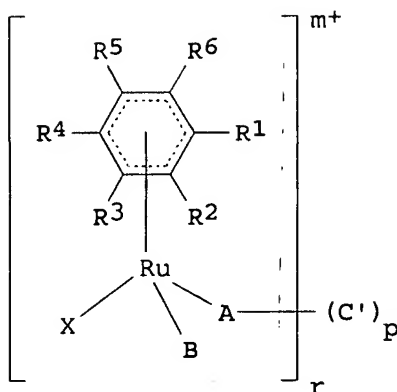
ACCESSION NUMBER: 2002:482176 CAPLUS
DOCUMENT NUMBER: 138:130575
TITLE: In vitro and in vivo activity and cross resistance profiles of novel ruthenium (II) organometallic arene complexes in human ovarian cancer
AUTHOR(S): Aird, R. E.; Cummings, J.; Ritchie, A. A.; Muir, M.; Morris, R. E.; Chen, H.; Sadler, P. J.; Jodrell, D. I.
CORPORATE SOURCE: Cancer Research UK, Edinburgh Oncology Unit, Western General Hospital, Edinburgh, EH4 2XR, UK
SOURCE: British Journal of Cancer (2002), 86(10), 1652-1657
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Organometallic ruthenium(II) arene anticancer complexes of the type [(η⁶-arene)Ru(II)(en)Cl][PF₆] (en = ethylenediamine) specifically target guanine bases of DNA oligomers and form monofunctional adducts. The structures of monofunctional adducts of the "piano-stool" complexes [(η⁶-Bip)Ru(II)(en)Cl][PF₆] (1, Bip = biphenyl), [(η⁶-THA)Ru(II)(en)Cl][PF₆] (2, THA = 5,8,9,10-tetrahydroanthracene), and [(η⁶-DHA)Ru(II)(en)Cl][PF₆] (3, DHA = 9,10-dihydroanthracene) with guanine derivs., were determined in the solid state by x-ray crystallog., and in solution using 2D [1H,1H] NOESY and [1H,15N] HSQC NMR methods. Strong π-π arene-nucleobase stacking is present in the crystal structures of [(η⁶-C14H14)Ru(en)(9EtG-N7)][PF₆]·2(MeOH) (6) and [(η⁶-C14H12)Ru(en)(9EtG-N7)][PF₆]·2(MeOH) (7) (9EtG = 9-ethylguanine). The anthracene outer ring (C) stacks over the purine base at distances of 3.45 Å for 6 and 3.31 Å for 7, with dihedral angles of 3.3° and 3.1°, resp. In the crystal structure of [(η⁶-biphenyl)Ru(en)(9EtG-N7)][PF₆]·2(MeOH) (4), there is intermol.

stacking between the pendant Ph ring and the purine six-membered ring at a distance of 4.0 Å (dihedral angle 4.5°). This stacking stabilizes a cyclic tetramer structure in the unit cell. The guanosine (Guo) adduct [(η6-biphenyl)Ru(en)(Guo-N7)][PF6]2·3.75(H2O) (5) exhibits intramol. stacking of the pendant Ph ring with the purine five-membered ring (3.8 Å, 23.8°) and intermol. stacking of the purine six-membered ring with an adjacent pendant Ph ring (4.2 Å, 23.0°). These occur alternately giving a columnar-type structure. A syn orientation of arene and purine is present in the crystal structures 5, 6, and 7, while the orientation is anti for 4. However, in solution, a syn orientation predominates for all the biphenyl adducts 4, 5, and the GMP (5'-GMP) adduct 8 [(η6-biphenyl)Ru(II)(en)(5'-GMP-N7)], as revealed by NMR NOE studies. The predominance of the syn orientation both in the solid state and in solution can be attributed to hydrophobic interactions between the arene and purine rings. There are significant reorientations and conformational changes of the arene ligands in [(η6-arene)Ru(II)(en)(G-N7)] complexes in the solid state, with respect to those of the parent chloro-complexes [(η6-arene)Ru(II)(en)Cl]+. The arene ligands have flexibility through rotation around the arene-Ru π-bonds, propeller twisting for Bip, and hinge-bending for THA and DHA. Thus propeller twisting of Bip decreases by ca. 10° so as to maximize intra- or intermol. stacking with the purine ring, and stacking of THA and DHA with the purine is optimized when their tricyclic ring systems are bent by ca. 30°, which involves increased bending of THA and a flattening of DHA. This flexibility makes simultaneous arene-base stacking and N7-covalent binding compatible. Strong stereospecific intramol. H-bonding between an en NH proton oriented away from the arene (en NH(d)) and the C6 carbonyl of G (G O6) is present in the crystal structures of 4, 5, 6, and 7 (average N...O distance 2.8 Å, N-H...O angle 163°). NMR studies of the 5'-GMP adduct 8 provided evidence that en NH(d) protons are involved in strong H-bonding with the 5'-phosphate and O6 of 5'-GMP. The strong H-bonding from G O6 to en NH(d) protons partly accounts for the high preference for binding of [(η6-arene)Ru(II)en]2+ to G vs. A (adenine). These studies suggest that simultaneous covalent coordination, intercalation, and stereospecific H-bonding can be incorporated into Ru(II) arene complexes to optimize their DNA recognition behavior, and as potential drug design features.

ACCESSION NUMBER: 2002:159911 CAPLUS
DOCUMENT NUMBER: 136:355324
TITLE: Organometallic Ruthenium(II) Diamine
Anticancer Complexes: Arene-Nucleobase
Stacking and Stereospecific Hydrogen-Bonding in
Guanine Adducts
AUTHOR(S): Chen, Haimei; Parkinson, John A.; Parsons, Simon;
Coxall, Robert A.; Gould, Robert O.; Sadler, Peter J.
CORPORATE SOURCE: Department of Chemistry, University of Edinburgh,
Edinburgh, EH9 3JJ, UK
SOURCE: Journal of the American Chemical Society (2002),
124(12), 3064-3082
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:355324
REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT



I

AB The preparation of compds. [I; wherein R1 and R2 together with the ring to which they are bound represent a saturated or unsatd. carbocyclic or heterocyclic group; R3, R4, R5, R6, independently = H, alkyl, aryl, alkaryl, or CO₂R' (R' = alkyl, aryl, or alkaryl); X = halo, H₂O, sulfoxy, carboxy, etc.; A and B, independently = O-donor, N-donor, or S-donor ligands, or halo; C' = (C1-C12)alkylene, optionally substituted in or on the alkylene chain, bound to two A groups; p = 0, 1 and r = 1 when p = 0 and r = 2 when p = 1; m = 0, 1] is described. Thus, 1,4,9,10-tetrahydroanthracene is reacted with RuCl₃•3H₂O to give 89% [(η⁶-C14H12)RuCl₂]₂, which was complexed with ethylenediamine (en) in the presence of NH₄PF₆ to give 33% [(η⁶-C14H12)RuCl(en)]+PF₆⁻. Compds. I are useful as antitumor agents, exhibiting IC₅₀ values as high as 315μM against A2780 ovarian cancer cell line. Biol. data are given.

ACCESSION NUMBER: 2002:31461 CAPLUS
DOCUMENT NUMBER: 136:85944
TITLE: Half-sandwich ruthenium
(II) compounds comprising heteroatom containing
ligands for treatment of cancer
INVENTOR(S): Morris, Robert Edward; Sadler, Peter John; Jodrell,
Duncan; Chen, Haimei
PATENT ASSIGNEE(S): University Court, the University of Edinburgh, UK
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002002572	A1	20020110	WO 2001-GB2824	20010626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2414446	A1	20020110	CA 2001-2414446	20010626
EP 1294732	A1	20030326	EP 2001-945472	20010626
EP 1294732	B1	20040818		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

BR 2001012122	A	20030513	BR 2001-12122	20010626
JP 2004502696	T	20040129	JP 2002-507824	20010626
AT 273985	T	20040915	AT 2001-945472	20010626
PT 1294732	T	20041231	PT 2001-945472	20010626
ES 2227225	T3	20050401	ES 2001-1945472	20010626
US 2004029852	A1	20040212	US 2003-312940	20030815
US 6936634	B2	20050830		

PRIORITY APPLN. INFO.:

GB 2000-16052	A	20000630
WO 2001-GB2824	W	20010626

OTHER SOURCE(S): MARPAT 136:85944

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 30 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Inhibition of the growth of the human ovarian cancer cell line A2780 by organometallic ruthenium(II) complexes of the type $[(\eta^6\text{-arene})\text{Ru}(\text{X})(\text{Y})(\text{Z})]$, where arene is benzene or substituted benzene, X, Y, and Z are halide, acetonitrile, or isonicotinamide, or X,Y is ethylenediamine (en) or N-ethylethylenediamine, has been investigated. The x-ray crystal structures of the complexes $[(\eta^6\text{-p-cymene})\text{Ru}(\text{en})\text{Cl}]\text{PF}_6$ (I), $[(\eta^6\text{-p-cymene})\text{RuCl}_2(\text{isonicotinamide})]$, and $[(\eta^6\text{-biphenyl})\text{Ru}(\text{en})\text{Cl}]\text{PF}_6$ are reported. They have "piano stool" geometries with η^6 coordination of the arene ligand. Complexes with X,Y as a chelated en ligand and Z as a monofunctional leaving group had the highest activity. Some complexes were as active as carboplatin. Hydrolysis of the reactive Ru-Cl bond in I was detected by HPLC but was suppressed by the addition of chloride ions. I binds strongly and selectively to G bases on DNA oligonucleotides to form monofunctional adducts. No inhibition of topoisomerase I or II by complex I was detected. These chelated Ru(II) arene complexes have potential as novel metal-based anticancer agents with a mechanism of action different from that of the Ru(III) complex currently on clin. trial.

ACCESSION NUMBER: 2001:719202 CAPLUS

DOCUMENT NUMBER: 136:15044

TITLE: Inhibition of Cancer Cell Growth by Ruthenium
(II) Arene Complexes

AUTHOR(S): Morris, Robert E.; Aird, Rhona E.; Murdoch, Piedad del Socorro; Chen, Haimei; Cummings, Jeff; Hughes, Nathan D.; Parsons, Simon; Parkin, Andrew; Boyd, Gary; Jodrell, Duncan I.; Sadler, Peter J.

CORPORATE SOURCE: Department of Chemistry, University of Edinburgh, Edinburgh, EH9 3JJ, UK

SOURCE: Journal of Medicinal Chemistry (2001), 44(22), 3616-3621

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

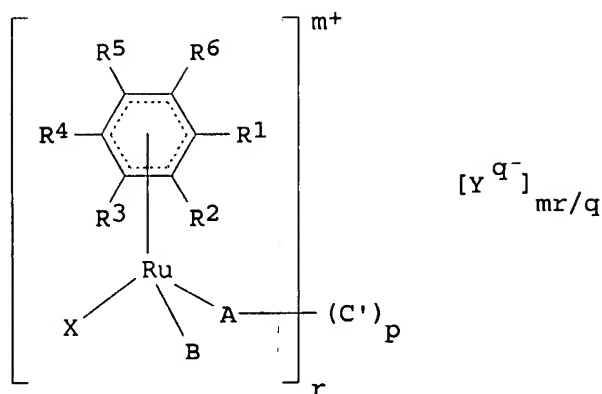
DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

GI



AB Title compds. I (R1, R2, R3, R4, R5, R6 = H, alkyl, -CO2R', aryl, alkylaryl, which latter two groups are optionally substituted on the aromatic ring; R' = alkyl, aryl, alkaryl; X = halo, H2O, (R')(R'')SO, R'CO2-, (R')(R'')C:O; R'' = alkyl, aryl, alkaryl; Y = counterion; m = 0-1; q = 1-3; C' = C1-12 alkylene, optionally substituted in or on the alkylene chain, bound to two A groups; p = 0-1 and r = 1 when p is 0 and r is 2 when p is 1; and A and B are: each independently N-donor nitrile ligands; or B is halo and A is an N-donor pyridine ligand, optionally substituted at one or more of the carbon atoms of the pyridine ring; or p is 0, A is NR7R8 and B is NR9R10, wherein R7, R8, R9 and R10 independently represent H or alkyl, and A and B are linked by an alkylene chain, optionally substituted in or on the alkylene chain; or p is 1, A is NR7 and B is NR9R10, wherein R7, R9 and R10 are as previously defined, and A and B are linked by an alkylene chain, optionally substituted) were prepared which may be used in the treatment and/or prevention of cancer.

ACCESSION NUMBER: 2001:319903 CAPLUS
DOCUMENT NUMBER: 134:326632
TITLE: Half-sandwich ruthenium
(II) compounds comprising nitrogen containing ligands
for treatment of cancer
INVENTOR(S): Morris, Robert Edward; Sadler, Peter John; Chen,
Haimei; Jodrell, Duncan
PATENT ASSIGNEE(S): The University Court, the University of Edinburgh, UK
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030790	A1	20010503	WO 2000-GB4144	20001026
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1224192	A1	20020724	EP 2000-971599	20001026
EP 1224192	B1	20050831		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2003512471	T	20030402	JP 2001-533142	20001026
AT 303393	T	20050915	AT 2000-971599	20001026
ES 2248136	T3	20060316	ES 2000-971599	20001026
US 2003023088	A1	20030130	US 2002-134404	20020426

US 6750251	B2	20040615		
US 2004220166	A1	20041104	US 2004-848416	20040518
US 6979681	B2	20051227		
US 2005239765	A1	20051027	US 2005-165372	20050623
PRIORITY APPLN. INFO.:			GB 1999-25274	A 19991027
			GB 2000-16054	A 20000630
			WO 2000-GB4144	W 20001026
			US 2002-134404	A1 20020426
			US 2004-848416	A1 20040518

OTHER SOURCE(S): MARPAT 134:326632
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 32 CAPLUS COPYRIGHT 2007 ACS on STN

AB Metal complexes and their pharmaceutical compns. are provided which have activity against diseases caused by, or are related to, overprod. of localized high concentration of reactive oxygen species, including nitric oxide, in the body. The neutral or charged complexes, which have at least one site for coordination of NO, consist of $[Ma(XbL)cYdZe]n_{\pm}$ wherein: M is a metal ion or a mixture of metal ions; X is a cation or a mixture of cations; L is a ligand, or mixture of ligands each containing at least two different donor atoms selected from the elements of Group IVA, Group VA or Group VIA of the Periodic Table; Y is a ligand or a mixture of the same or different ligands each containing at least one donor atom or more than one donor atom selected from the elements of Group IVA, Group VA or Group VIA of the Periodic Table; and Z is a halide or pseudohalide ion or a mixture of halide ions and pseudohalide ions; and wherein: a = 1-3; b = 0-12; c = 0-18; d = 0-18; e = 0-18; and n = 0-10; provided that at least one of c, d and e is ≥ 1 ; wherein c is 0, b is also 0; wherein a is 1, c, d and e are ≤ 9 ; and wherein a is 2, c, d and e are ≤ 12 . A wide variety of preferred ligands are presented, e.g., polyaminocarboxylates, dithiocarbamates, pyridinethionato, etc. The preparation of >100 example complexes of ruthenium are presented. In vitro cell culture tests (murine (RAW264) macrophage cell lines) and ex vivo tests (vasoconstriction of rat tail artery) demonstrated the lowering of nitric oxide levels by the complexes. The complexes inhibit tumor growth in a mammalian subject. Complexes $[Ru(Hedta)]H_2O$ (AMD 6245, edta = ethylenediaminetetraacetate) and $K[Ru(H_2dtpa)Cl]H_2O$ (AMD 6221, dtpa = diethylenetriaminepentaacetate) inhibited the growth of P22 carcinosarcoma in rat. This was associated with a decrease in tumor blood supply and a decrease in plasma NO levels.

ACCESSION NUMBER: 2000:688243 CAPLUS
DOCUMENT NUMBER: 133:260767
TITLE: Pharmaceutical compositions comprising metal complexes for removal of excess nitric oxide and other reactive oxygen species in mammals
INVENTOR(S): Fricker, Simon; Abrams, Michael J.; Bridger, Gary; Skerlj, Renato; Baird, Ian; Cameron, Beth R.
PATENT ASSIGNEE(S): Anormed Inc., Can.
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056743	A1	20000928	WO 2000-CA294	20000317
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW			

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
 DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 CA 2367282 A1 20000928 CA 2000-2367282 20000317
 EP 1163247 A1 20011219 EP 2000-910468 20000317
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO
 BR 2000011678 A 20020226 BR 2000-11678 20000317
 US 2002049190 A1 20020425 US 2000-527450 20000317
 JP 2004500321 T 20040108 JP 2000-606604 20000317
 HU 200400457 A2 20040528 HU 2004-457 20000317
 NO 2001004526 A 20011016 NO 2001-4526 20010918
 PRIORITY APPLN. INFO.: US 1999-125166P P 19990319
 WO 2000-CA294 W 20000317
 REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
119.98	214.75

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-24.96	-36.66

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NEWS	3	JAN 16	CA/CAPLUS Company Name Thesaurus enhanced and reloaded
NEWS	4	JAN 16	IPC version 2007.01 thesaurus available on STN
NEWS	5	JAN 16	WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS	6	JAN 22	CA/CAPLUS updated with revised CAS roles
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NEWS	8	JAN 29	PHAR reloaded with new search and display fields
NEWS	9	JAN 29	CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS	10	FEB 15	PATDPASPC enhanced with Drug Approval numbers
NEWS	11	FEB 15	RUSSIAPAT enhanced with pre-1994 records
NEWS	12	FEB 23	KOREAPAT enhanced with IPC 8 features and functionality
NEWS	13	FEB 26	MEDLINE reloaded with enhancements
NEWS	14	FEB 26	EMBASE enhanced with Clinical Trial Number field
NEWS	15	FEB 26	TOXCENTER enhanced with reloaded MEDLINE
NEWS	16	FEB 26	IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS	17	FEB 26	CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
NEWS	18	MAR 15	WPIDS/WPIX enhanced with new FRAGHITSTR display format
NEWS	19	MAR 16	CASREACT coverage extended
NEWS	20	MAR 20	MARPAT now updated daily
NEWS	21	MAR 22	LWPI reloaded
NEWS	22	MAR 30	RDISCLOSURE reloaded with enhancements
NEWS	23	APR 02	JICST-EPLUS removed from database clusters and STN
NEWS	24	APR 30	GENBANK reloaded and enhanced with Genome Project ID field
NEWS	25	APR 30	CHEMCATS enhanced with 1.2 million new records
NEWS	26	APR 30	CA/CAPLUS enhanced with 1870-1889 U.S. patent records
NEWS	27	APR 30	INPADOC replaced by INPADOCDB on STN
NEWS	28	MAY 01	New CAS web site launched
NEWS	29	MAY 08	CA/CAPLUS Indian patent publication number format defined
NEWS	30	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS EXPRESS		NOVEMBER 10	CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.
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